

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Marc Feldmann and Ravinder N. Maini  
Serial No. : Not Yet Known  
Filed : Herewith  
For : ANTI-TNF ANTIBODIES AND METHOTREXATE IN THE  
TREATMENT OF TNF-MEDIATED DISEASE

1185 Avenue of the Americas  
New York, New York 10036  
August 3, 2001

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination, please make the following amendments to the  
above-identified application:

In the Specification

Please delete the paragraph on page 1, lines 5-15, and insert the  
following:

This application is a continuation of U.S. Serial No.  
08/690,775, filed August 1, 1996, which is a continuation-  
in-part of U.S. Serial No. 08/607,419, filed February 28,  
1996, now abandoned, which is a continuation-in-part of PCT  
International Application No. PCT/GB94/00462, filed March  
10, 1994, which is a continuation-in-part of U.S. Serial  
No. 08/403,785, now U.S. Patent No. 5,741,488, based on PCT

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International Application No. PCT/GB93/02070, filed October 6, 1992, which is a continuation-in-part of U.S. Serial No. 07/958,248, filed October 8, 1992, now abandoned, the teachings of all of which are incorporated herein by reference.

### In the Claims

Please cancel claims 1-31 without prejudice to applicants' right to pursue the subject matter of these claims in a continuing application.

Please add new claims 32-69 as follows:

32. (New) A method for treating or preventing a tumor necrosis factor-mediated disease in an individual in need thereof comprising co-administering methotrexate and a TNF $\alpha$  antagonist to said individual, in therapeutically effective amounts.
33. (New) The method of Claim 32, wherein said TNF $\alpha$  antagonist and methotrexate are administered simultaneously.
34. (New) The method of Claim 32, wherein said TNF $\alpha$  antagonist and methotrexate are administered sequentially.
35. (New) The method of Claim 32, wherein the tumor necrosis factor-mediated disease is selected from the group consisting of autoimmune disease, acute or chronic immune disease, inflammatory disease and neurodegenerative disease.

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36. (New) The method of Claim 35, wherein said TNF $\alpha$  antagonist is administered in multiple doses.
37. (New) The method of Claim 32, wherein said TNF $\alpha$  antagonist prevents or inhibits TNF $\alpha$  synthesis or TNF $\alpha$  release.
38. (New) The method of Claim 37, wherein said TNF $\alpha$  antagonist is a phosphodiesterase inhibitor.
39. (New) The method of Claim 38, wherein said phosphodiesterase inhibitor is selected from the group consisting of pentoxifylline and rolipram.
40. (New) The method of Claim 37, wherein said TNF $\alpha$  antagonist is selected from the group consisting of thalidomide and tenidap.
41. (New) The method of Claim 38, wherein said TNF $\alpha$  antagonist is selected from the group consisting of an A2b adenosine receptor agonist and an A2b adenosine receptor enhancer.
42. (New) The method of Claim 36, wherein said TNF $\alpha$  antagonist is an anti-TNF $\alpha$  antibody or antigen-binding fragment thereof.
43. (New) The method of Claim 42, wherein said anti-TNF $\alpha$  antibody or antigen-binding fragment is a chimeric antibody or chimeric fragment, said chimeric antibody or chimeric fragment comprising a non-human variable region specific for TNF $\alpha$  or an antigen-binding portion thereof and a human

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constant region.

44. (New) The method of Claim 43, wherein said chimeric antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.
45. (New) The method of Claim 44, wherein said chimeric antibody competitively inhibits binding of TNF $\alpha$  to monoclonal antibody cA2.
46. (New) The method of Claim 44, wherein said chimeric antibody is monoclonal antibody cA2.
47. (New) The method of Claim 42, wherein said anti-TNF $\alpha$  antibody is a humanized antibody or antigen-binding fragment thereof.
48. (New) The method of Claim 47, wherein said humanized antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.
49. (New) The method of Claim 42, wherein said anti-TNF $\alpha$  antibody is a resurfaced antibody or antigen-binding fragment thereof.
50. (New) The method of Claim 49, wherein said resurfaced antibody binds to one or more epitopes included in amino acid residues set forth in SEQ ID NO:1 or SEQ ID NO:2.
51. (New) The method of Claim 36, wherein said TNF $\alpha$  antagonist is a soluble TNF $\alpha$  receptor or functional portion thereof.

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52. (New) The method of Claim 51, wherein said soluble TNF $\alpha$  receptor is selected from the group consisting of p55 TNF $\alpha$  receptor and p75 TNF $\alpha$  receptor.
53. (New) The method of Claim 51, wherein said soluble TNF $\alpha$  receptor is a TNF $\alpha$  receptor multimeric molecule.
54. (New) The method of Claim 51, wherein said soluble TNF $\alpha$  receptor is a TNF $\alpha$  receptor immunoreceptor fusion molecule
55. (New) A method for treating or preventing arthritis in an individual in need thereof comprising co-administering methotrexate and a TNF $\alpha$  antagonist to said individual, in therapeutically effective amounts.
56. (New) The method of Claim 55, wherein said TNF $\alpha$  antagonist and methotrexate are administered simultaneously.
57. (New) The method of Claim 55, wherein said TNF $\alpha$  antagonist and methotrexate are administered sequentially.
58. (New) The method of Claim 55, wherein said TNF $\alpha$  antagonist is administered in multiple doses.
59. (New) The method of Claim 55, wherein said TNF $\alpha$  antagonist prevents or inhibits TNF $\alpha$  synthesis or TNF $\alpha$  release.
60. (New) A method for treating or preventing rheumatoid arthritis in an individual in need thereof comprising co-administering methotrexate and a TNF $\alpha$  antagonist to said

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individual, in therapeutically effective amounts.

61. (New) The method of Claim 60, wherein said TNF $\alpha$  antagonist and methotrexate are administered simultaneously.
62. (New) The method of Claim 60, wherein said TNF $\alpha$  antagonist and methotrexate are administered sequentially.
63. (New) The method of Claim 60, wherein said TNF $\alpha$  antagonist is administered in multiple doses.
64. (New) The method of Claim 60, wherein said TNF $\alpha$  antagonist prevents or inhibits TNF $\alpha$  synthesis or TNF $\alpha$  release.
65. (New) A method for treating or preventing Crohn's disease in an individual in need thereof comprising co-administering methotrexate and a TNF $\alpha$  antagonist to said individual, in therapeutically effective amounts.
66. (New) The method of Claim 65, wherein said TNF $\alpha$  antagonist and methotrexate are administered simultaneously.
67. (New) The method of Claim 65, wherein said TNF $\alpha$  antagonist and methotrexate are administered sequentially.
68. (New) The method of Claim 65, wherein said TNF $\alpha$  antagonist is administered in multiple doses.
69. (New) The method of Claim 65, wherein said TNF $\alpha$  antagonist prevents or inhibits TNF $\alpha$  synthesis or TNF $\alpha$  release.

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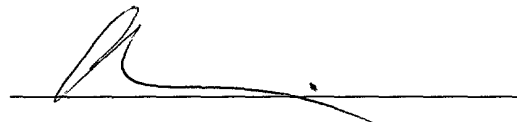
**REMARKS**

This application is a continuation of U.S. Serial No. 08/690,775, filed August 1, 1996. The '775 Application is due to issue as U.S. Patent No. 6,270,766 on August 7, 2001. Accordingly, the '775 application is pending today, and this continuation application is being timely filed.

By this Preliminary Amendment, applicants have amended the specification to incorporate a priority claim to parent application U.S. Serial No. 08/690,775. Applicants have also canceled claims 1-31 without prejudice and have added new claims 32-69 to introduce certain format changes. Accordingly new claims 32-69 are pending in the subject application.

No fee, other than the enclosed \$1,114.00 application filing fee, is deemed necessary in connection with the filing of this Preliminary Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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